Research Protocol

Title: Ocular Sarcoidosis Open Label Trial of ACTHAR Gel

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Investigator initiated study (IIS) Form

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Amendment	4

1. Title of Study:

Ocular Sarcoidosis Open Label Trial of ACTHAR Gel

2. Hypothesis:

Treatment with ACTHAR Gel will result in a reduction of ocular inflammation in patients with active ocular sarcoidosis that requires systemic immunosuppressant therapy

3. Rationale for the study:

The initial treatment of ocular sarcoidosis usually relies on a combination of topical glucocorticoids and oral glucocorticoids, both of which are associated with significant ocular and systemic toxicities. Steroid-sparing therapies are limited by variable and unpredictable efficacy, prolonged time until clinical response, medication intolerance, and difficulties obtaining payor approval. As a result, it is not uncommon that treating physicians must choose between excessive glucocorticoid toxicity versus poor control of ocular inflammation. Ongoing ocular inflammation, in turn, leads to eventual visual loss and occasionally blindness.
There is a need for a more reliable, expeditious therapy that can be used as an alternative to glucocorticoids in sarcoidosis uveitis. Adrenocorticotropic hormone, through activation of melanocortin receptors on leukocytes, can dampen immune responses through non-glucocorticoid dependent mechanisms. The proposed study will aim to define whether there is effectiveness for ACTHAR gel in these patients, delineate an effect dosing regimen, and provide information about the safety of this approach for moderate to severe ocular sarcoidosis.

ACTHAR is a 39-amino acid peptide natural form of adrenocorticotropin hormone (ACTH) that was initially approved in 1952 by the FDA. It has since been approved for 19 indications including respiratory sarcoidosis, multiple sclerosis, and infantile spasms.

4. Patient Population and Estimated Sample Size:

Patients with sarcoidosis (as defined by ATS/ERS/WASOG criteria) who have moderate to severe ocular sarcoidosis, defined as:

1. Any posterior, intermediate or panuveitis of sufficient severity to warrant therapy, in the opinion of the treating physician –OR—

2. Anterior uveitis requiring 4 or more daily applications of topical corticosteroids to maintain control of inflammation.

We propose to enroll patients, at the Cleveland Clinic, until at least 20 patients have successfully completed 4 weeks of therapy in this open label trial in order to determine effect size, speed of response and tolerability. In the event the Cleveland Clinic is unsuccessful in recruiting a sufficient number of subjects additional sites may be added as needed.

Statistical Analysis: The proof of concept patient population will consist of patients with ocular sarcoidosis. The definition of condition improvement is such that the patients will be classified under any of the following:

a) Improved visual acuity (by at least one grade)
b) Resolution of intraocular inflammation (no more than trace cells)
c) Tapering of ocular or oral steroids by at least 50%
d) Reduction of cystoid macular edema (graded by the ophthalmologist)
e) No worsening of any of the above

Given these conditions, the acceptance of a compost endpoint and an assumption that that only 20% of those with intraocular sarcoidosis will spontaneously remit or improve on the composite endpoint in the time-frame of the study, inclusion of 20 patients confers an 87% power to identify a 50% response rate from the medication at a two-sided alpha error rate of 0.05

The Cleveland Clinic will oversee the study, and maintain responsibility for collection of the case report forms and analysis of the data.

Study Design:

Inclusion/Exclusion Criteria

Inclusion Criteria

- Patient with sarcoidosis as defined by ATS/ERS/WASOG guidelines
- Any posterior, intermediate or panuveitis of sufficient severity to warrant therapy, in the opinion of the treating physician --OR-- Anterior uveitis requiring 4 or more daily applications of topical corticosteroids to maintain control of inflammation, or uncontrolled with topical therapy
- Persistent disease activity (active uveitis) at the time of screening

Exclusion criteria

- Other cause for ocular inflammation
- Uncontrolled diabetes, hypertension, or other contra-indication to increased dosage of glucocorticoids

- Recent (less than 4 weeks) intra-ocular or intra-orbital steroid injection
- Escalation of immunosuppressive medications between screening and initiation of the study medication
- Severe extra-ocular sarcoidosis likely to require additional therapy (in the opinion of the investigator)
- Administration of an investigational medication for sarcoidosis within 3 months, or 5 half-lives, whichever is longer
- Have a history of any opportunistic infection within 6 months prior to screening
- Have any history of malignancy, except fully resected cutaneous squamous cell cancer or cutaneous basal cell cancer, or cervical carcinoma in-situ with a minimum of 5 years period without recurrence
- Severe other organ disease felt to be likely to lead to death within the next six months
- Unable to follow the study protocol, including the requisite travel and follow-up ocular testing
- Women of childbearing potential must be using adequate birth control measures (abstinence, hormonal contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) and must agree to continue such precautions, and not become pregnant or plan a pregnancy for 6 months after receiving their last treatment with study agent. Women of childbearing potential must test negative on a serum pregnancy test at screening.
- Breastfeeding women are excluded from participation

Study Procedures

Baseline assessments:

- Ocular exam (including visual acuity, intraocular pressure, cell count, vitreous haze assessment); visual analogue assessment of vision
- Retinal angiography and optical coherence tomography; (if not performed within the previous 4 weeks).
- Sarcoidosis Health Questionnaire Ocular module (SHQO)
- Fatigue Assessment Scale (FAS)
- King's Sarcoidosis Health Questionnaire (KSHQ)
- Blood draw for biomarkers;
- Extra-ocular organ involvement (WASOG instrument)

Treatment with ACTHAR Gel for 24 weeks

- Initial treatment with 80 units daily for ten days (induction phase)
- Maintenance treatment with 80 units twice weekly (maintenance phase)
- In the event of substantial side-effects deemed to be probably related to ACTHAR gel by the investigator; the dose may be reduced to 40 units twice weekly in subjects who have controlled inflammation.
- If they are not showing any evidence of improvement after 4 weeks, then the medication will be discontinued and management will be at the discretion of the treating physician.

	Screen	Week 0	Week 2	Week 4	Week 6	Week 8	Week 12	Week 18	Week 24	Week 36	Week 48
Informed Consent	X										
Focused H&P	X	X		X		X	X	X	X	X	X

	Screen	Week 0	Week 2	Week 4	Week 6	Week 8	Week 12	Week 18	Week 24	Week 36	Week 48
Ophthalmologic exam	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure	X	X	X	X	X	X	X	X	X	X	X
Visual acuity (Snellen)	X	X	X	X	X	X	X	X	X	X	X
Retinal angiography		X		X			X		X		X
Optical coherence tomography		X		X			X		X		X
Assess organ involvement	X	X		X			X	X	X	X	X
QOL instruments (FAS, KSHQ, SHQO)		X		X		X	X		X		X
Toxicity assessment			X	X	X	X	X	X	X	X	X
Medication list	X	X	X	X	X	X	X	X	X	X	X
Dispense medication		X		X		X	X	X	X	X	
Inflammatory biomarkers (serum draw for freezing)		X		X		X	X	X	X		X
Patient stipend	X	X	X	X	X	X	X	X	X	X	X

Protocol for treatment failure

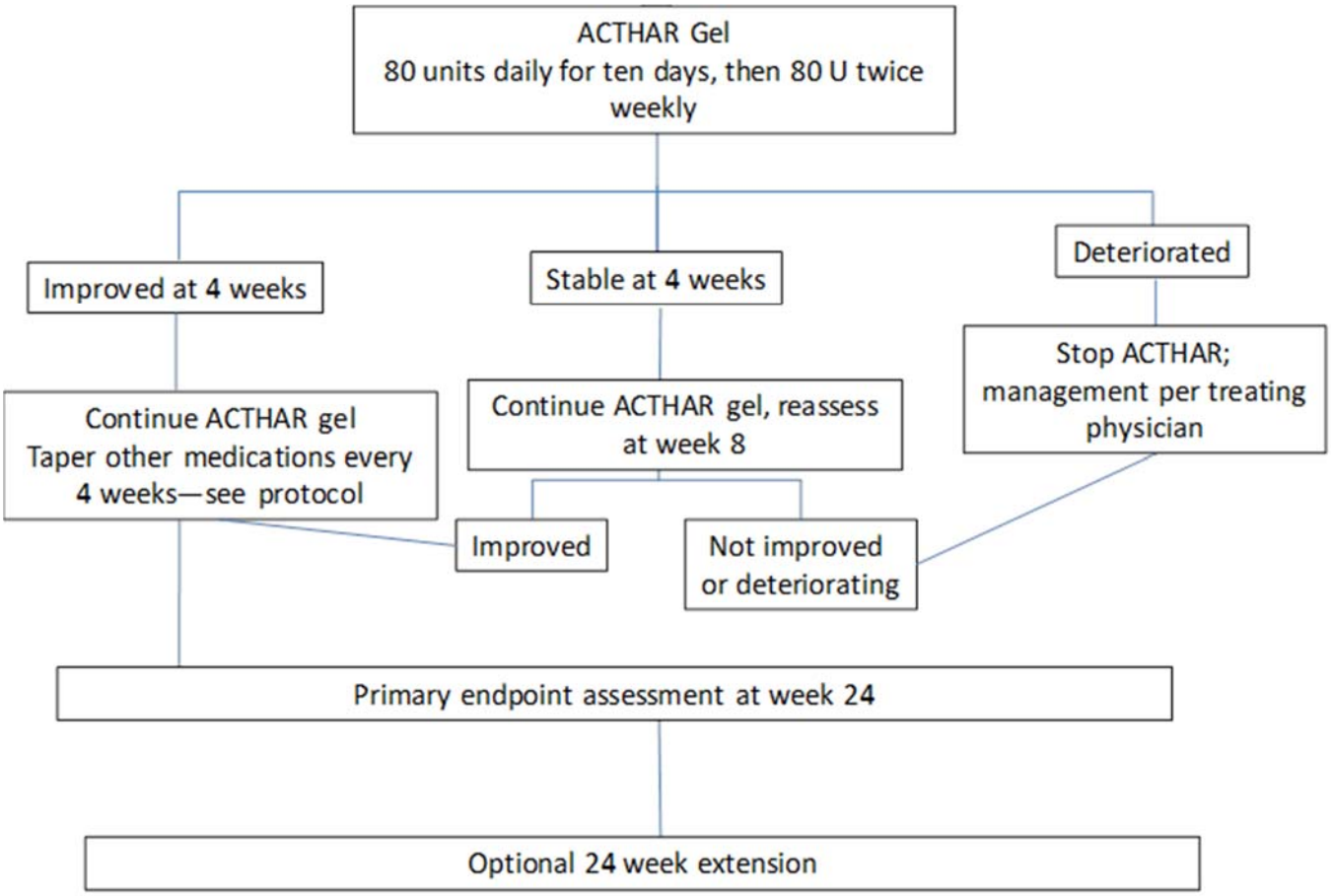
- Treatment failure will be defined as any of:
    - Two step increase from baseline in SUN activity (anterior chamber) grade on two consecutive readings, or increase from Grade 3 to Grade 4
    - Failure to demonstrate improvement by 12 weeks in subjects with baseline SUN Grade ≥ 2
    - Failure to demonstrate any improvement by week 24 in SUN Grade 0-1+
    - Significant worsening of vitritis, retinal vasculitis, or macular edema associated with reduction of visual acuity
    - No improvement of vitritis, retinal vasculitis, or macular edema by week 12 in subjects with more than trace vitreous cells
- In the event of worsening inflammation during prednisone tapering, the dose of prednisone will be increased to the last dose level for an additional 4 weeks, prior to resumption of the tapering schedule
- In the event of treatment failure prior to the prednisone tapering phase, or in the event that the subject requires a second prednisone escalation, the subject will be dropped from the trial, and management of uveitis will be at the discretion of the treating physician.

Criteria for drug interruption or discontinuation

- Uncontrolled hyperglycemia requiring hospitalization, leading to other complications, or unable to be controlled with anti-diabetic medications
- Vision-threatening elevation of intraocular pressure unable to manage with topical anti-glaucoma therapy
- Infections requiring hospitalization (medication may be resumed after the infection is

resolved)

- Other severe medical complications deemed to be likely associated with study medication in the opinion of the investigator



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5. Primary end-point:

(Measured at 24 weeks):

Proportion of patients meeting the composite of improvement of any one of the following variables, with no worsening of any single one, and no need for additional sarcoidosis therapies:

- visual acuity
- resolution of intraocular inflammation
- tapering of ocular or oral steroids by at least 50%
- reduction of cystoid macular edema

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6. Secondary end-points:

- Proportion of patients meeting the primary endpoint at 4, 8 and 12 weeks
- Toxicity (including intraocular pressure)

- Durability of effectiveness (out to 48 weeks)
- Quality of life
- Inflammatory biomarkers
- Extra- ocular organ activity

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7. Estimated time line (including contracting, IRB approval, study initiation, enrollment, study completion and submission of publication):

Thirty-six months, including six months to complete contracting and protocol development, 24 months for patient recruitment and study, and six months for data analysis and manuscript submission

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8. Adverse Events and Data Monitoring

The risks of ACTHAR include and are not limited to those seen with glucocorticoid use. Acthar Gel causes the release of endogenous cortisol from the adrenal gland. Therefore all the adverse effects known to occur with elevated cortisol may occur with Acthar Gel administration as well. Common adverse reactions include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

Substantial side effects related to ACTHAR gel could include infection requiring parenteral antibiotics or any opportunistic infection; diabetes that cannot be controlled with conventional therapy; fluid retention that cannot be controlled with conventional diuretics; mood or personality changes deemed in the opinion of the investigator to require dose reduction.

The subject will undergo a focused history and physical examination at nine study assessment dates. The appropriate laboratory and ocular studies will be obtained as per the timeline. The study coordinator will contact patients by phone during the induction period. Adverse events that take place during the testing or afterwards will be recorded along with the patient's data and will be reported directly to the IRB by the PI. A data monitor will be assigned to the study.

All tests are routinely performed here at the Cleveland Clinic. The risks of each procedure are minimal.

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9. Ethical considerations

Recruitment

We propose to enroll patients, at the Cleveland Clinic, until at least 20 patients have successfully completed 4 weeks of therapy in this open label trial in order to determine effect size, speed of response and tolerability. In the event the Cleveland Clinic is unsuccessful in recruiting a sufficient number of subjects additional sites may be added as needed. These sites may include

- UCMC University of Cincinnati, Robert Baughman
- Albany Medical Center, Marc Judson
- Mount Sinai New York, Adam Morgenthau or Doug Jabs
- University of Miami, Victor Perez

- Oregon Health and Sciences University, James Rosenbaum
- National Jewish Medical Center, Nabeel Hamzeh
- University of Alabama-Birmingham, Joseph Barney

Compensation will be provided for patients in the form of a stipend for each completed study visit.

Risks/Benefits

The benefits of the study would be to provide evidence that ACTHAR gel may serve as a therapeutic immune-modulating alternative to glucocorticoids in patients with ocular sarcoidosis. Risks of the study include known side effects of glucocorticoid therapy as well as infection requiring parenteral antibiotics or any opportunistic infection; diabetes that cannot be controlled with conventional therapy; fluid retention that cannot be controlled with conventional diuretics; mood or personality changes deemed in the opinion of the investigator to require dose reduction.

Informed Consent

Patients recruited from the existing sarcoidosis population at the Cleveland Clinic and meet inclusion criteria will be consented during their regularly scheduled visit with the investigator. For patients who meet the inclusion criteria that are self-referred or referred by their physicians, a screening visit will be scheduled at which time they will be consented.

No vulnerable subjects will be included.

10. Study Organization and Results

The Cleveland Clinic will oversee the study and maintain responsibility for collection of the case report forms and analysis of the data. If necessary, subcontracts will be negotiated directly between Questcor and the individual sites and Questcor will be responsible for shipping medication directly to the study sites.

We anticipate presentation of the results of this trial at the American Thoracic Society and the American Academy of Ophthalmology. We will aim to publish the results in a society journal, with the choice dependent on the outcome of the trial.